REMARKS

Supplemental Material:

Applicants have provided additional material with this Amendment and Response in the form of a 37 CFR 1.132 Declaration. The material consists of experiments performed the process described in the instant application. The experiments show delivery of a therapeutic polynucleotides encoding VEGF (vascular endothelial growth factor) and EPO (erythropoietin), i.e. polynucleotides other than DNA encoding a marker protein, to limb skeletal muscle cells. The experiments introduce no new matter.

Election/Restriction

The action states that the Application contains claims 4 and 40. In an amendment file May 3, 2002, Applicants elected Group I claims 1-39. In an amendment filed June 13, 2002, Applicants elected Group I claims 1-3 and 5-39. In the amendments filed August 11, 2003 and December 22, 2003, claims 4 and 40 were indicated as withdrawn.

Rejection of the claims under 35 USC § 112

Claims 1 and 39 have been rejected under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement. Applicants have amended the claim to recite "an injector selected from the group consisting of needle and catheter". Injection using a needle is supported in example 8 on page 31. Injection using a catheter is supported in example 1 on page 23 and in example 3 on page 25.

Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 have been rejected under 35 U.S.C 112. Applicants have amended independent claims 1 and 39 to more clearly set forth that the polynucleotides are delivered to skeletal muscle cells of the limb into which they are injected. The action states that the claims are not limited to delivering the polynucleotide to a cell in the same limb as it is injected and suggests that the claim should recite delivering the polynucleotide to muscle cells in "said limb" (page 6 of the action) Previously amended claims 1 and 39 both recited "delivering the polynucleotides to skeletal muscle cells in the limb" (underline added) which is equivalent to "said limb."

Claims 1 and 39 have also been amended to more clearly set forth delivery of polynucleotides to muscle cells that are located distal to the occlusion. The amended claim further clarifies the relationship between the location of the occlusion, site of injection, and location of muscles

cells to which the polynucleotides are delivered. Support for delivery of polynucleotides to muscle cells in the limb distal to the occlusion can be found on page 32 lines 18-19. Support for delivery to all muscle groups in the limb distal to the occlusion can be found in the examples. For injection into rhesus monkey, injection and occlusion were located just above the elbow or knee (example 1). Delivery, as evidenced by luciferase expression, was then observed in muscles throughout the lower limb (example 3). In animals in which the occlusion was located higher on the hind limb, polynucleotide delivery was observed in muscles of the upper leg as well as the lower leg and foot (example 10). Support for injection into an artery is found in the specification on page 6 lines 4-5, page 10 line 21, and in examples 1, 3, 7, 8, 9 and 10.

The action states on page 7 that the specification only enables delivering DNA encoding a marker protein operable linked to a promoter. Applicants respectfully disagree. A gene encoding a therapeutic gene, or a gene whose effect on a cell is being investigated, is functionally equivalent to a marker gene for the purposes of delivery using the described invention; see page 9 lines 13-18. In addition, delivery of the therapeutic gene, human factor IX, to limb skeletal muscle cells is shown in example 8 on page 31. While delivery in this example is performed without a cuff, the example demonstrates the equivalence of polynucleotides encoding marker genes and therapeutic genes (or other genes of research or intellectual interest). As further evidence of enablement of delivery of polynucleotides encoding therapeutic protein, Applicants submit Supplemental Information showing delivery of polynucleotides encoding VEGF and EPO. The delivery of the polynucleotides was done using the same method as described in the specification.

The action states that the Applicants' previous arguments regarding RNA and antisense are moot because they are not under consideration. Applicants respectfully disagree. RNA and antisense polynucleotides are polynucleotides, they can be delivered using the described invention, they do not need to be operably linked to a promoter, and they can elicit an effect in a cell without being expressed. Therefore, they do address the issue of whether "for delivery to have an enabled use, it must encode a protein this is expressed to detectable levels in the cell."

The action states, on pages 5 and 8, that Miller, Deonarain, Verma and Crystal establish that at the time of filing, the ability to target the desired tissue was unpredictable. The instant

application was filed on November 2000 and is related to a provisional filed November 1999. Miller was published in 1995, Deonarain in 1998, Verma in 1997, and Crystal in 1995. The Examiner further acknowledges that neither Miller, Deonarain, Verma or Crystal teach the process taught be the Applicants. Applicants do not find it reasonable to state that no advance can have been made or method invented and that prior documents, which do not teach or contemplate the process taught by the Applicants, can be given sufficient weight to indicate the Applicants' process can not work. The Applicants' process is clearly shown to be able to deliver polynucleotides to limb skeletal muscle cells. Furthermore, the Examiner acknowledged that the Applicants' process is enabling for "a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a marker protein operably linked to a promoter and wherein said marker protein is expressed to detectable levels in muscles of said limb" (Office Actions dated October 27, 2003 and July 30, 2002 and February 18, 2004).

Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 have been rejected under 35 U.S.C 112, second paragraph, as being indefinite. Applicants have amended claims 1 and 39, as recommended by the Examiner, to more clearly set forth that blood flow to the mammalian limb is occluded and to more clearly set forth the method of the occlusion. Claim 39 has been amended to more clearly set forth that the blood vessel is part of the animal.

Support for "applying a device for impeding blood flow to the surface of the skin of said limb" in claim 1 can be found on page 3 lines 8-24, on page 5 lines 13-24 and in the examples 1 and 10.

Support for "applying sufficient pressure against said limb with said device to form an occlusion of blood flow to said limb" in claim 1 can be found on page 3 lines 8-24, on page 5 lines 13-24 and in the examples 1 and 10.

Support for "consists of a cuff surrounding said limb" in claim 35 can be found on page 5 lines 5-11, page 23 lines 22-25 and page 25 lines 19-21.

Support for "wherein the pressure occludes blood flow through said blood vessel and is applied to the skin of said limb by a device external to the skin of said mammal" in claim 39 can be found on page 3 lines 8-24, on page 5 lines 13-24 and in the examples 1 and 10.

Rejection of the claims under 35 USC § 102

Claims 1, 3, 33-35 and 39 have been rejected under 35 U.S.C. 102(b) as being anticipated by Milas *et al.* 1997. The action states that the limitation of "for delivering polynucleotides to (a) skeletal muscle cell(s)" in is not an intended use and does not bear patentable weight because it may not occur. Applicants respectfully disagree and direct attention to step c) of previously amended claim 1 (step (d) of currently amended claim 1) and step b) of claim 39. The action further states that the method of Milas inherently results in delivery of adenovirus to skeletal muscle and provides as evidence fig. 3 on page 2200. Applicants respectfully disagree and direct attention to the legend describing fig. 3. Fig. 3 of Milas shows the location of labeled red blood cells during the procedure. The figure does not show adenovirus nor does the figure show any delivery of any component out of the vasculature.

The action further states that the delivery methods of Milas are indistinguishable from the Applicants' claims. Applicants respectfully disagree. Milas taught perfusing adenovirus through the vasculature of an isolated limb using two catheters, one in the artery and one in the vein. Perfusion, with outflow, is required by Milas (paragraph 1 on page 2202). In contrast, Applicants' claims require only injection into a blood vessel and inherently results in no outflow. "Resultant brisk outflow" as taught by Milas is equivalent to not impeding blood flow as taught by the Applicants. Failure to impede blood flow, as taught by the Applicants, results in failure to efficiently deliver polynucleotides to skeletal muscle cells, page 30 lines 23-24.

Double patenting rejection:

The claims have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 09/707,117. Applicants will file a terminal disclaimer upon allowance of claims should the examiner determine a terminal disclaimer is still necessary.

Claims 1-3, 37 and 39 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No.

6,379,966. Applicants respectfully disagree. 6,379,966 did not teach or contemplate applying a non-invasive cuff to the surface of the mammal's skin.

The claims have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/917,154. Applicants respectfully disagree. 09/917,154 did not teach or contemplate applying a non-invasive cuff to the surface of the mammal's skin.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 should be allowable. Applicants respectfully request a timely Notice of Allowance be issued in the case.

Respectfully submitted,

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I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as express mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this date: 6/16/04.

Kirk Ekena